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UTILITY PATENT APPLICATION TRANSMITTAL

(For new Non-provisional applications under 37 CFR 1.53(b))

Attorney Docket No.: _____
First Named Inventor: Ian L. Scott
Express Mail Label EL307223385US

Box PATENT APPLICATION
Assistant Commissioner For Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is a new utility patent application of inventor(s): Ian L. Scott, Bore G. Raju, Ronald J. Biediger, Vanessa O. Grabbe, Jamal M. Kassir, Karin M. Keller, Timothy P. Kogan, Shuqun Lin and Robert V. Market: "Compounds That Inhibit The Binding of Integrins To The Receptors"

Application Elements:

1. **[X]** Specification containing 45 pages (preferred arrangement set forth below)
   - -- Descriptive Title of the Invention
   - -- Cross-reference to related applications (if applicable)
   - -- Statement regarding Federally-sponsored Research & Development (if applicable)
   - -- Reference to Microfiche Appendix (if applicable);
   - -- Background of the Invention
   - -- Brief Summary of the Invention
   - -- Brief Description of the Drawings (if filed)
   - -- Detailed Description
   - -- Claim(s)
   - -- Abstract of the Disclosure

2. [ ] Drawings: [ ] Sheets of [ ] formal drawings [ ] informal drawings

3. Oath or Declaration
   a. **[X]** An unexecuted declaration or oath for the utility patent application including a power of attorney,
   b. [ ] A copy from a prior application (37 CFR 1.63(d), for continuation with No. 16 completed).
      i. [ ] Signed statement attached deleting inventor(s) named in the prior application (see 37 CFR 1.63(d)(2) and 1.33(b).

4. [ ] Incorporation by Reference (useable if Box 3b is checked) - The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 3b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

5. [ ] Microfiche Computer Program (Appendix)

6. [ ] Nucleotide and/or Amino Acid Sequence submission. including:
   [ ] Computer readable copy,
   [ ] Paper copy (identical to computer copy),
   [ ] Statement verifying identity of above copies.

Accompanying Application Parts:

7. [ ] Assignment Papers (cover sheet, document(s), and requisite fee ($40.00 for each property of each conveyance or transfer)).

8. [ ] 37 CFR 3.73(b) Statement (where there is an assignee)
   [ ] Power of Attorney

9. [ ] English Translation document (if applicable)

10. [ ] Information Disclosure Statement (IDS), including PTO-1449
    [ ] Copies of IDS Citations

11. [ ] Preliminary Amendment

12. [X] Return Postcard for PTO Mail Room Date Stamp (should be specifically itemized).

13. [X] Unexecuted Small Entity Statement(s)
    [ ] Statement filed in prior application, status still proper and desired.

14. [ ] Certified Copy of Priority Document(s) (if foreign priority is claimed).

15. [ ] Other _____

16. [X] **If Continuing Application**, check appropriate box and supply the requisite information:
    [ ] Continuation [ ] Divisional [x] Continuation-in-part (CIP) of prior application No. 60/082,019.

FEE CALCULATION

The fee has been calculated as shown below:

				Small Entity			Large Entity	
FOR	No. Filed	No. Allowed	No. Extra	Rate	Fee	OR	Rate	Fee
Basic Fee					$395.00	OR		$790.00
Total Claims	10	20 =		x$11.00	$	OR	$22.00	$
Independent Claims	1	1 =		x $41.00	$	OR	$82.00	$
Multiple Dep. Claims				+ $135.00	$	OR	+ $$270.00	$
Other Fees				$	$	OR	$	$
				TOTAL	$395.00	OR	TOTAL	$

17. [x] A check in the amount of $ 395.00 to cover the filing fee is enclosed.

18. [ ] Please charge my Deposit Account No. 04-1644 in the amount of $_____.

19. [X] The Commissioner is authorized to charge payment of the following amounts associated with this communication or credit any overpayment to Deposit Account No. 04-1644:
    a. [X] Additional filing fees under 37 CFR 1.16 or deficiencies in remittances therefor.
    b. [X] Additional processing fees under 37 CFR 1.17 or deficiencies in remittances therefor.
    c. [X] **ONLY if applicant has partially paid** the patent issue fee under 37 C.F.R. §1.18, then the **deficiency** shall be charged to Deposit Account No. 04-1644, and the Commissioner if authorized to so charge the Deposit Account.

Date: April 15, 1999 Attorney's Signature _____
Martin L. Katz, Reg. No. 25,011

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CERTIFICATE OF EXPRESS MAIL

I hereby certify that this Utility Patent Application Transmittal, enclosed application, and any other documents referred to as enclosed herein, are being deposited in an envelope with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated below and addressed to Box PATENT APPLICATION, Assistant Commissioner for Patents, Washington, D.C. 20231.

EL307223385US
Express Mail Label No.

April 15, 1999
Date of Deposit

Elaine M. Ramesh
Typed or Printed Name of Person Mailing Correspondence

Elaine M Ramesh
Signature of Person Mailing Correspondence

Applicant or Patentee: Scott et al. Atty Docket No. _____
Serial or Patent No.: _____
Filed or Issued: _____
For: Compounds That Inhibit The Binding of Integrins To The Receptor

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS

(37 C.F.R. 1.9(f) AND 1.27(c) - SMALL BUSINESS CONCERN)

I hereby declare that I am

[ ] the owner of the small business concern identified below:

[X] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: Texas Biotechnology Corporation
ADDRESS OF CONCERN: 7000 Fannin Street, Suite 1920
Houston, TX 77030 USA

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 C.F.R. 121.12, and reproduced in 37 C.F.R. 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled: Compounds That Inhibit The Binding of Integrins to The Receptors by inventor(s): Ian L. Scott, Bore G. Raju, Ronald J. Biediger, Vanessa O. Grabbe, Jamal M. Kassir, Karin M. Keller, Timothy P. Kogan, Shuqun Lin and Robert V. Market described in:

[ ] the specification filed herewith.

[X] Application Serial No. _____, filed April 15, 1999.

[ ] Patent No. _____, issued _____.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern, or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 C.F.R. 1.9(c) if that person had made the invention, or by any concern which would not qualify as a small business concern under 37 C.F.R. 1.9(d) or a nonprofit organization under 37 C.F.R. 1.9(e). *NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 C.F.R 1.27)

NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: David B. McWilliams
TITLE OF PERSON OTHER THAN OWNER: President and CEO
ADDRESS OF PERSON SIGNING: 7000 Fannin Street, Suite 1920, Houston, TX 77030USA

SIGNATURE: _____ DATE: _____

COMPOUNDS THAT INHIBIT THE BINDING OF INTEGRINS TO THEIR RECEPTORS

Cross-Reference to Related Application

This application is a continuation-in-part of co-pending U.S. Provisional Application No. 60/082019, filed April 16, 1998.

Field of the Invention

This invention is directed generally to the inhibition of the binding of $\alpha_4\beta_1$ integrin to its receptors, for example VCAM-1 (vascular cell adhesion molecule-1) and fibronectin. The invention also relates to compounds that inhibit this binding; to pharmaceutically active compositions comprising such compounds; and to the use of such compounds either as above, or in formulations for the control or prevention of disease states in which $\alpha_4\beta_1$ is involved.

Background of the Invention

When a tissue has been invaded by a microorganism or has been damaged, white blood cells, also called leukocytes, play a major role in the inflammatory response. One of the most important aspects of the inflammatory response involves the cell adhesion event. Generally, white blood cells are found circulating through the bloodstream. However, when a tissue is infected or becomes damaged, the white blood cells recognize the invaded or damaged tissue, bind to the wall of the capillary and migrate through the capillary into the affected tissue. These events are mediated by a family of proteins called cell adhesion molecules.

There are three main types of white blood cells: granulocytes, monocytes and lymphocytes. The integrin $\alpha_4\beta_1$ (also called VLA-4 for very late antigen-4) is a heterodimeric protein expressed on the surface of monocytes,

lymphocytes and two subclasses of granulocytes: eosinophils and basophils. This protein plays a key role in cell adhesion through its ability to recognize and bind VCAM-1 and fibronectin, proteins associated with the endothelial cells that line the interior wall of capillaries.

Following infection or damage of tissue surrounding a capillary, endothelial cells express a series of adhesion molecules, including VCAM-1, that are critical for binding the white blood cells that are necessary for fighting infection. Prior to binding to VCAM-1 or fibronectin, the white blood cells initially bind to certain adhesion molecules to slow their flow and allow the cells to "roll" along the activated endothelium. Monocytes, lymphocytes, basophils and eosinophils are then able to firmly bind to VCAM-1 or fibronectin on the blood vessel wall *via* the $\alpha_4\beta_1$ integrin. There is evidence that such interactions are also involved in transmigration of these white blood cells into the damaged tissue as well as the initial rolling event itself.

Although white blood cell migration to the site of injury helps fight infection and destroy foreign material, in many instances this migration can become uncontrolled, with white blood cells flooding to the scene, causing widespread tissue damage. Compounds capable of blocking this process, therefore, may be beneficial as therapeutic agents. Thus, it would be useful to develop inhibitors that would prevent the binding of white blood cells to VCAM-1 and fibronectin.

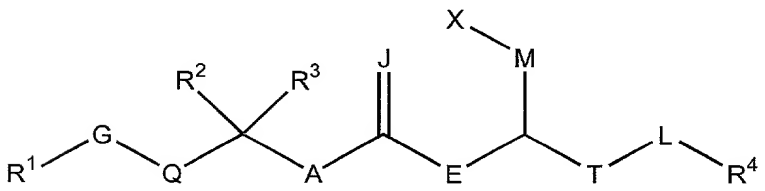
Some of the diseases that might be treated by the inhibition of $\alpha_4\beta_1$ binding include, but are not limited to, atherosclerosis, rheumatoid arthritis, asthma, allergy, multiple sclerosis, lupus, inflammatory bowel disease, graft rejection, contact hypersensitivity, and type I diabetes. In addition to being found on some white blood cells, $\alpha_4\beta_1$ is also found on various cancer cells, including leukemia, melanoma, lymphoma and sarcoma cells. It has been suggested that cell adhesion involving $\alpha_4\beta_1$ may be involved in the metastasis of certain cancers. Inhibitors of $\alpha_4\beta_1$ binding may, therefore, also be useful in the treatment of some forms of cancer.

The isolation and purification of a peptide which inhibits the binding of $\alpha_4\beta_1$ to a protein is disclosed in U.S. Patent No. 5,510,332. Peptides which inhibit binding are disclosed in WO 95/15973, EP 0 341 915, EP 0 422 938 A1, U.S. Patent No. 5,192,746 and WO 96/06108. Novel compounds which are useful for inhibition and prevention of cell adhesion and cell adhesion-mediated pathologies are disclosed in WO 96/22966, WO 98/04247 and WO 98/04913.

It is therefore an object of the invention to provide novel compounds which are inhibitors of $\alpha_4\beta_1$ binding, and pharmaceutical compositions including such novel compounds.

Brief Summary of the Invention

The present invention is directed to compounds of formula I



Formula I

wherein A is selected from the group consisting of O, S, and NR^5;

E is selected from the group consisting of CH_2, O, S, and NR^6;

Q is selected from the group consisting of C(O) and $(CH_2)_k$ wherein k is an integer of 0 or 1;

J is selected from the group consisting of O, S and NR^8;

G is selected from the group consisting of O, NH, S, and $(CH_2)_p$ wherein p is an integer of 0 or 1;

T is selected from the group consisting of C(O) and $(CH_2)_b$ wherein b is an integer of from 0 to 3;

L is selected from the group consisting of O, NR^7, S, and $(CH_2)_n$ wherein n is an integer of 0 or 1;

M is selected from the group consisting of $C(R^9)(R^{10})$ and $(CH_2)_u$, wherein u is an integer of from 0 to 3;

X is selected from the group consisting of CO_2B, PO_3H_2, SO_3H, OPO_3H_2, $C(O)NHC(O)R^{11}$, $C(O)NHSO_2R^{12}$, tetrazolyl and hydrogen;

B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy, cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl, heterocyclyl, heterocyclylalkyl and alkylheterocyclyl groups;

wherein R^2 and R^3 taken together may form a ring;

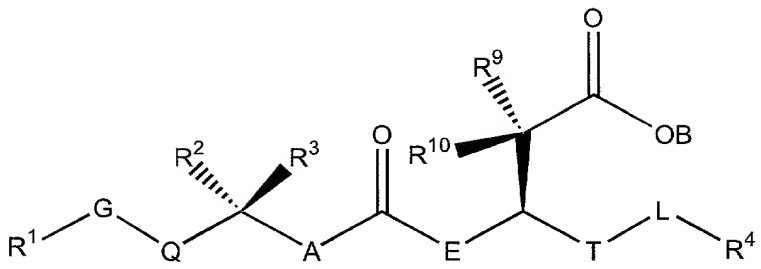
R^4 and R^7 taken together may form a ring;

R^9 and R^{10} taken together may form a ring;

and salts and optical isomers thereof.

For Formula I, presently preferred compounds may have R^1, R^2 and R^3 independently as hydrogen, alkoxy, alkoxyalkoxy, aryl, alkylaryl, arylalkyl, heterocyclyl or alkyl; R^4 as aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl or heterocyclylalkyl; X as CO_2B; and M as $C(R^9)(R^{10})$ wherein R^9 and R^{10} are independently hydrogen or lower alkyl.

More specifically, the compounds of this invention may be described by Formula II



Formula II

wherein the substituents are as defined for Formula I,

and the pharmaceutically acceptable salts and prodrugs thereof.

For Formula II, presently preferred compounds may have R^1, R^2 and R^3 independently as hydrogen, alkoxy, alkoxyalkoxy, aryl, alkylaryl, arylalkyl, heterocyclyl or alkyl; R^4 as aryl, alkylaryl, arylalkyl, heterocyclyl, heterocyclylalkyl or alkyheterocyclyl; R^5 and R^6 if present as hydrogen; and R^9 and R^{10} independently as hydrogen or lower alkyl.

Preferred compounds have the following substituents: R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl and alkyl; R^4 is selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclylalkyl, alkylheterocyclyl and heterocyclyl; R^5 and R^6 if present are hydrogen; X is CO_2B and B is independently selected from the group consisting of hydrogen and lower alkyl.

Presently preferred compounds are (3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-3-(methylsulfanyl)-1-((phenylsulfanyl)methyl)propyl)amino) carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-2-((cyclopropylmethyl)thio)-1-((phenylthio)methyl)ethyl)amino)carbonyl) amino)propanoic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-{[(2-thienylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(3-hydroxy-4-

methoxybenzyl)amino]carbonyl}-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({4-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl) methyl]propyl}amino)carbonyl] amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino) carbonyl]amino}propanoic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[({4-[(2-methylbenzyl)amino]benzyl} amino)carbonyl]-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({3-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl)methyl] propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylthio)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino} propanoic acid, (9S, 13S)-13-(1,3-benxodioxol-5-yl)-3,11-dioxo-1-phenyl-9-(((4-((2-toluidinocarbonyl)amino)benzyl)amino)carbonyl)-2-oxa-4, 10,12-triazapentadecan-15-oic acid and pharmaceutically acceptable salts, optical isomers and pro-drugs thereof.

The present invention also relates to pharmaceutical compositions comprising a physiologically acceptable diluent and at least one compound of the present invention.

The present invention further relates to a process of inhibiting the binding of $\alpha_4\beta_1$ integrin to VCAM-1 comprising exposure of a cell expressing $\alpha_4\beta_1$ integrin to a cell expressing VCAM-1 in the presence of an effective inhibiting amount of a compound of the present invention. The VCAM-1 may be on the surface of a vascular endothelial cell, an antigen presenting cell, or other cell type. The $\alpha_4\beta_1$ may be on a white blood cell such as a monocyte, lymphocyte, granulocyte; a stem cell; or any other cell that naturally expresses $\alpha_4\beta_1$.

The invention also provides a method for treating disease states mediated by $\alpha_4\beta_1$ binding which comprises administration of an effective amount

of a compound of the present invention, either alone or in formulation, to an afflicted patient.

Detailed Description of the Invention

As used herein, the term "alkyl" means straight or branched, saturated or unsaturated carbon chains having up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. As used herein, this term is meant to encompass alkenyl and alkynyl groups. "Lower alkyl" refers to C_1-C_6 alkyl.

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings, including, but not limited to cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, and adamantyl among others. As used herein, this term is meant to encompass alkenyl and alkynyl groups. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a lower alkyl radical, including, but not limited to cyclohexylmethyl.

The term "halo" or "halogen" as used herein refers to I, Br, Cl or F.

The term "haloalkyl" as used herein refers to a lower alkyl radical, to which is appended at least one halogen substituent, for example chloromethyl, fluoroethyl, trifluoromethyl and pentafluoroethyl among others.

The term "alkoxy" as used herein refers to R_aO- wherein R_a is a lower alkyl group. Examples of alkoxy include, but are not limited to, ethoxy, tert-butoxy, among others.

The term "alkoxyalkoxy" as used herein refers to R_bO-R_cO- wherein R_b is lower alkyl as defined above and R_c is alkylene wherein alkylene is -$(CH_2)_{n'}$- wherein n' is an integer from 1 to 6. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy, among others.

The term "alkylamino" as used herein refers to R_dNH- wherein R_d is a lower alkyl group, for example, ethylamino, butylamino, among others.

The term "carboxy" as used herein refers to a carboxylic acid radical, -C(O)OH.

The term "amino" as used herein refers to H_2N- .

As used herein, the term "aryl" means a carbocyclic aromatic group, as for example phenyl, naphthyl, indenyl, indanyl, anthracenyl, among others.

The term "heterocyclyl" refers to an aromatic or non-aromatic cyclic group having one or more oxygen, nitrogen or sulfur atoms in the ring, as for example, furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, indolinyl, benzo[b]furanyl, 2,3-dihydrobenzofuranyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzothiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxizinyl, tetrahydrofuranosyl, tetrahydropyranosyl, piperidinyl, piperazinyl, among others.

The term "heterocyclylalkyl" as used herein refers to a heterocyclyl group appended to a lower alkyl radical, including but not limited to 2-thienylmethyl, 2-pyridinylmethyl and 2-(1-piperidinyl) ethyl.

The term "alkylheterocyclyl" as used herein refers to an alkyl group appended to a heterocyclyl radical, including but not limited to 2-methyl-5-thiazolyl, 2-methyl-1-pyrrolyl and 5-ethyl-2-thiophenyl.

Suitable substituents for the aryl, alkyl, cycloalkyl, or heterocyclyl groups described above, when present, include alcohols, amines, heteroatoms, or any combination of aryl, alkoxy, alkoxyalkoxy, alkyl, cycloalkyl or heterocyclyl groups either attached directly, or *via* suitable linkers. The linkers are typically short chains of 1-3 atoms containing any combination of C, C=O, CO_2, O, N, or S, S=O, SO_2, as for example ethers, amides, amines, ureas, sulfamides, sulfonamides, among others.

For example, R^1, R^2 and R^3 in Formulas I and II above may independently be, but are not limited to, phenyl, thienylmethyl, isobutyl, n-butyl, 2-thienylmethyl, 1,3-thiazol-2-yl-methyl, benzyl, thienyl, 3-pyridinylmethyl, 3-methyl-1-benzothiophen-2-yl, allyl, isobutyl, 3-methoxybenzyl, propyl, 2-ethoxyethyl, cyclopropylmethyl, benzylsulfanylmethyl, benzylsulfonylmethyl, phenylsulfanylmethyl, phenethylsulfanylmethyl, 3-phenylpropylsulfanylmethyl, 4-((2-toluidinocarbonyl)amino)benzyl, 2-pyridinylethyl, 2-(1H-indol-3-yl)ethyl, 1H-benzimidazol-2-yl, 4-piperidinylmethyl, 3-hydroxy-4-methoxybenzyl, 4-hydroxyphenethyl, 4-aminobenzyl, phenylsulfonylmethyl, 4-(acetylamino)phenyl, 4-methoxyphenyl, 4-aminophenyl, 4-chlorophenyl, (4-(benzylsulfonyl)amino)phenyl, (4-(methylsulfonyl)amino)phenyl, 2-aminophenyl, 2-methylphenyl, isopropyl, isobutyl, 2-oxo-1-pyrrolidinyl, 3-(methylsulfanyl)propyl, (propylsulfanyl)methyl, octylsulfanylmethyl, 3-aminophenyl, 4-((2-toluidinocarbonyl)amino)phenyl, 2-((methylbenzyl)amino)benzyl, methylsulfanylethyl, or ethylsulfanylmethyl.

The R^4 substituent for formulas I and II above may be, but is not limited to 1,3-benzodioxol-5-yl, 1-naphthyl, thienyl, 4-isobutoxyphenyl, 2,6-dimethylphenyl, allyloxyphenyl, 3-bromo-4-methoxyphenyl, 4-butoxyphenyl, 1-benzofuran-2-yl, 2-thienylmethyl, phenyl, methylsulfanyl, phenylsulfanyl, phenethylsulfanyl, 4-bromo-2-thienyl, 3-methyl-2-thienyl, or 4,5-dihydro-1,3-oxazol-2-yl.

R^2 and R^3 may be linked to form a ring such as cyclopropyl, cyclopentyl, cyclobutyl, cyclohexyl, 4-piperidinyl, and 4-tetrahydropyranyl among others.

R^4 and R^7 may be linked to form a ring such 1-pyrrolidino, 1-piperidino, 4-methyl-1-piperazino, 4-acetyl-1-piperazino and 4-morpholino among others.

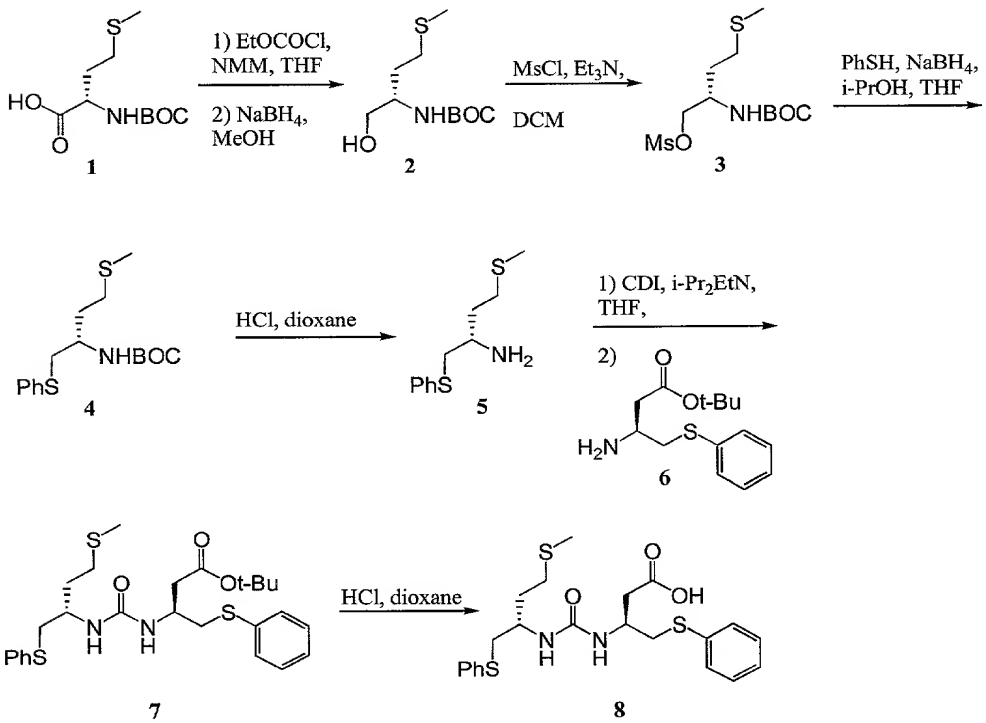
R^9 and R^{10} may be linked to form a ring such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl among others.

Abbreviations

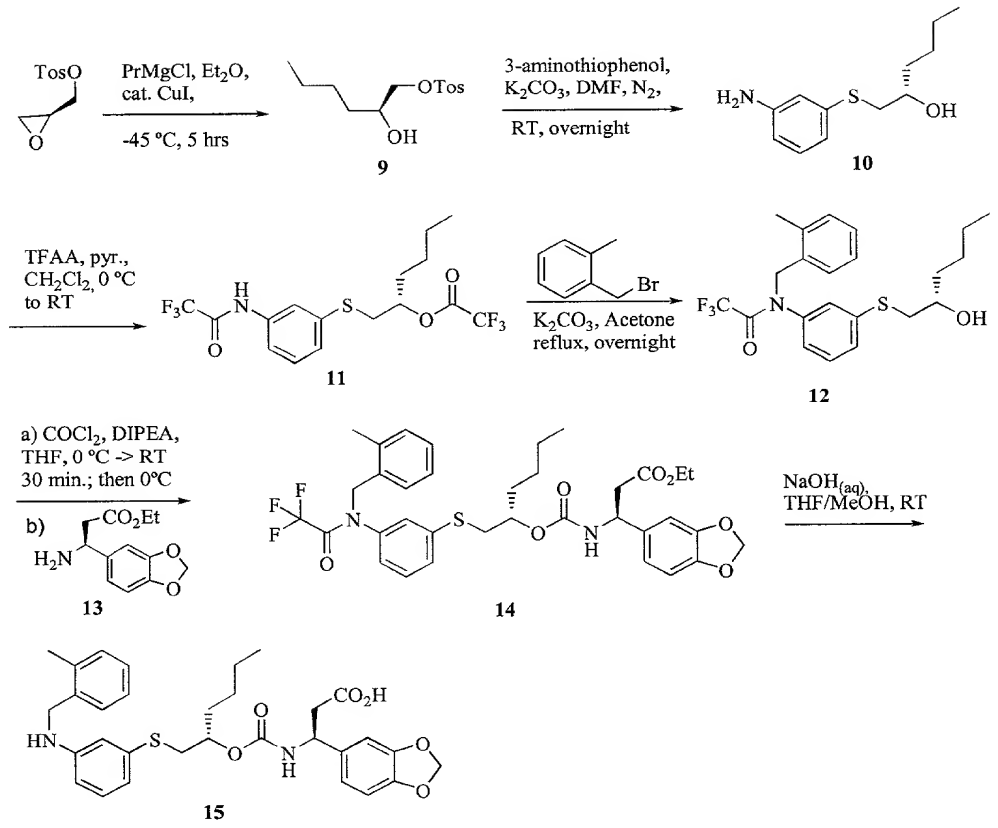
Abbreviations which have been used in the schemes and the examples which follow are: BOC for t-butyloxycarbonyl; EtOAc for ethyl acetate; DMF

for dimethylformamide; THF for tetrahydrofuran; Tos for p-toluenesulfonyl; DCC for dicyclohexylcarbodiimide; HOBT for 1-hydroxybenzotriazole; TFAA for trifluoroacetic anhydride; NMM for N-methyl morpholine; DIPEA for diisopropylethylamine; DCM for dichloromethane; CDI for 1,1'-carbonyldiimidazole; TBS for TRIS-buffered saline; EDCI for 1-(3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride; Ms for methane sulfonyl and Cbz for benzyloxycarbonyl. Amino acids are abbreviated as follows: C for L-cysteine; D for L-aspartic acid; E for L-glutamic acid; G for glycine; H for L-histidine; I for L-isoleucine; L for L-leucine; N for L-asparagine; P for L-proline; Q for L-glutamine; S for L-serine; T for L-threonine; V for L-valine and W for L-tryptophan.

Examples of procedures that may be used to synthesize compounds of formula I are given in Schemes 1-4. A detailed description of the preparation of representative compounds of the present invention is set forth in the Examples below.

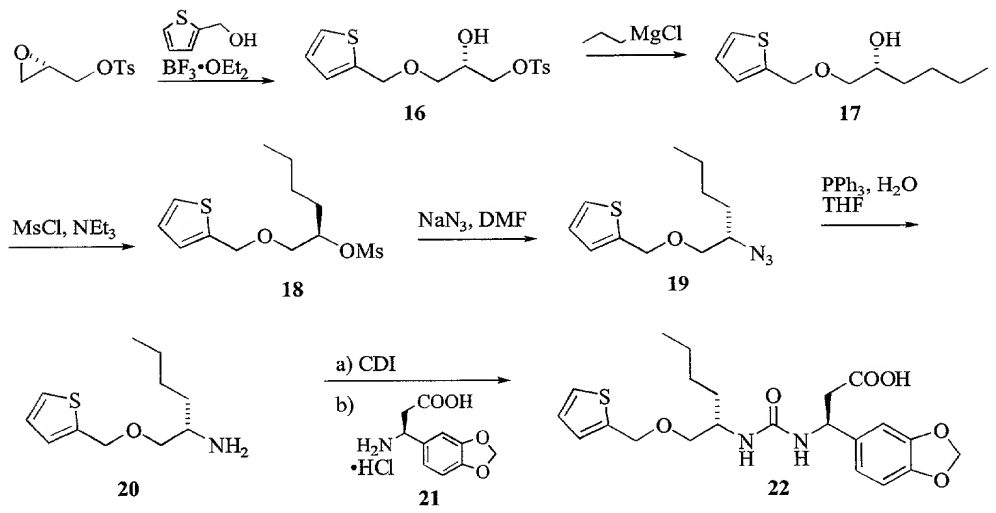


Scheme 1

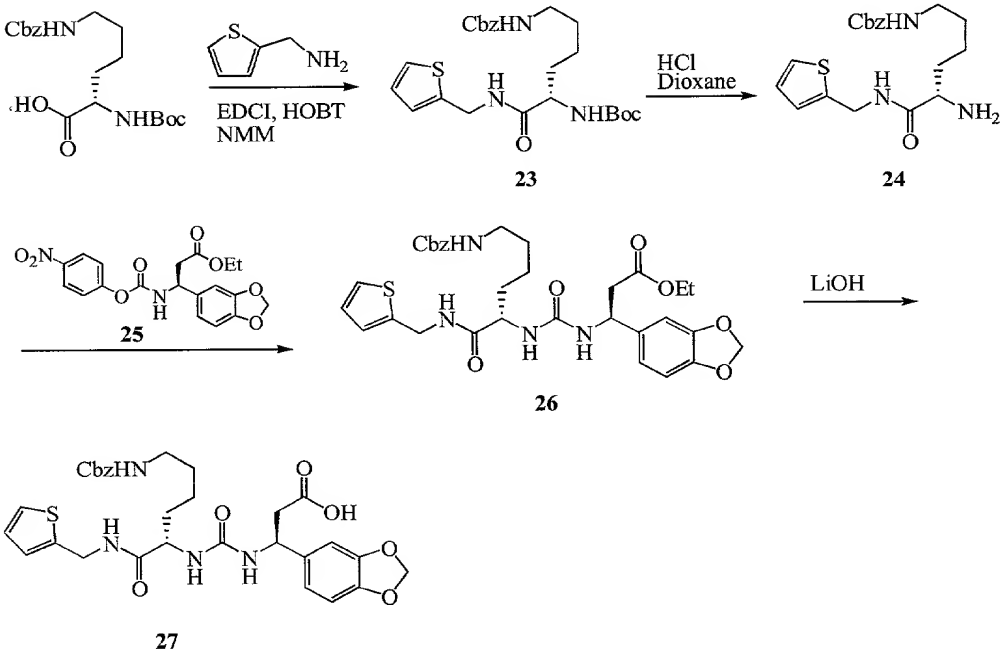

TosO
PrMgCl, Et2O,
cat. CuI,
-45 °C, 5 hrs
OTos
OH
9
3-aminothiophenol,
K2CO3, DMF, N2,
RT, overnight
H2N
S
OH
10
TFAA, pyr.,
CH2Cl2, 0 °C
to RT
F3C
H
N
O
S
O
CF3
11
Br
K2CO3, Acetone
reflux, overnight
12
a) COCl2, DIPEA,
THF, 0 °C -> RT
30 min.; then 0°C
b)
CO2Et
H2N
13
F
F
F
14
NaOH(aq),
THF/MeOH, RT
CO2H
HN
15

Scheme 2

5



Scheme 3



Scheme 4

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-

containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester

or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase "therapeutically effective amount" of the compound of the invention means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.0001 to about 1000 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range of from about 0.001 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The present invention also provides pharmaceutical compositions that comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be specially formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally , intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

In another aspect, the present invention provides a pharmaceutical composition comprising a component of the present invention and a physiologically tolerable diluent. The present invention includes one or more compounds as described above formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively referred to herein as diluents, for parenteral injection, for intranasal delivery, for oral administration in solid or liquid form, for rectal or topical administration, among others.

The compositions can also be delivered through a catheter for local delivery at a target site, *via* an intracoronary stent (a tubular device composed of a fine wire mesh), or *via* a biodegradable polymer. The compounds may also be complexed to ligands, such as antibodies, for targeted delivery.

Compositions suitable for parenteral injection may comprise physiologically acceptable, sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), vegetable oils (such as olive oil), injectable organic esters such as ethyl oleate, and suitable mixtures thereof.

These compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may

also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or

carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed,

groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms,

where possible, of the compounds of the invention. Prodrugs of the present invention may be rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987), hereby incorporated by reference.

Compounds of the present invention that are formed by *in vivo* conversion of a different compound that was administered to a mammal are intended to be included within the scope of the present invention.

Compounds of the present invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention.

In another aspect, the present invention contemplates a process of inhibiting the binding of $\alpha_4\beta_1$ integrin to VCAM-1. A process of the present

invention can be used either *in vitro* or *in vivo*. In accordance with a process of the present invention, a cell expressing $\alpha_4\beta_1$ integrin is exposed to a cell expressing VCAM-1 in the presence of an effective inhibiting amount of a compound of the present invention.

A cell expressing $\alpha_4\beta_1$ integrin can be a naturally occurring white blood cell, mast cell or other cell type that naturally expresses $\alpha_4\beta_1$ on the cell surface, or a cell transfected with an expression vector that contains a poly-nucleotide (e.g., genomic DNA or cDNA) that encodes $\alpha_4\beta_1$ integrin. In an especially preferred embodiment, $\alpha_4\beta_1$ integrin is present on the surface of a white blood cell such as a monocyte, a lymphocyte or a granulocyte (e.g., an eosinophil or a basophil).

A cell that expresses VCAM-1 can be a naturally occurring cell (e.g. an endothelial cell) or a cell transfected with an expression vector containing a polynucleotide that encodes VCAM-1. Methods for producing transfected cells that express VCAM-1 are well known in the art.

Where VCAM-1 exists on the surface of cell, the expression of that VCAM-1 is preferably induced by inflammatory cytokines such as tumor necrosis factor-α, interleukin-4 and interleukin-1β.

Where the cells expressing $\alpha_4\beta_1$ integrin and VCAM-1 are in a living organism, a compound of the present invention is administered in an effective amount to the living organism. Preferably, the compound is in a pharmaceutical composition of this invention. A process of the present invention is especially useful in treating diseases associated with uncontrolled migration of white blood cells to damaged tissue. Such diseases include, but are not limited to, asthma, atherosclerosis, rheumatoid arthritis, allergy, multiple sclerosis, lupus, inflammatory bowel disease, graft rejection, contact hypersensitivity, type I diabetes, leukemia, and brain cancer. Administration is preferably accomplished *via* intravascular, subcutaneous, intranasal, transdermal or oral delivery.

The present invention also provides a process of selectively inhibiting the binding of $\alpha_4\beta_1$ integrin to a protein comprising exposing the integrin to the

protein in the presence of an effective inhibiting amount of a compound of the present invention. In a preferred embodiment, the $\alpha_4\beta_1$ integrin is expressed on the surface of a cell, either naturally occurring or a cell transformed to express $\alpha_4\beta_1$ integrin.

The protein to which the $\alpha_4\beta_1$ integrin binds can be expressed either on a cell surface or be part of the extracellular matrix. Especially preferred proteins are fibronectin or invasin.

The ability of compounds of the present invention to inhibit binding is described in detail hereinafter in the Examples. These Examples are presented to desribe preferred embodiments and utilities of the invention and are not meant to limit the invention unless otherwise stated in the claims appended hereto.

Example 1

Synthesis of (3S)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl)amino)carbonyl]amino}-4-(phenylsulfanyl)butanoic acid (**8**)

Step One: N-Boc-L-Methionine **1** (2 g, 8 mmol) was dissolved in THF (40 mL) and the solution cooled to 0°C. N-Methylmorpholine (0.77 mL, 8 mmol) and ethyl chloroformate (0.88 ml, 8 mmol) were added and the mixture was stirred for 30 minutes while maintaining the low temperature. The mixture was quickly filtered and sodium borohydride (0.88 g, 23 mmol) was added. Methanol (100 mL) was added slowly to the ice-cold solution. The ice-bath was removed and the solution stirred at room temperature for 1 hour. A standard aqueous work-up gave the primary alcohol **2** (1.8 g, 95%).

Step Two: To an ice-cold solution of the alcohol **2** (1.8 g, 7.7 mmol) in methylene chloride (30 mL) was added triethylamine (1.6 mL, 11.5 mmol) and methanesulfonyl chloride (0.8 mL, 10.4 mmol). After 5 minutes, the reaction

was poured into water. A standard aqueous work-up gave the mesylate **3** (2.24 g, 93%).

Step Three: To a solution of the mesylate **3** (1 g, 3.2 mmol) in a mixture of THF (10 mL) and isopropanol (10 ml) was added thiophenol (0.33 mL, 3.2 mmol) and sodium borohydride (0.15 g, 3.9 mmol). The mixture was stirred at room temperature overnight. A standard aqueous work-up gave the sulfide **4** (0.94 g, 90%).

Step Four To a solution of the sulfide **4** (0.94 g, 2.9 mmol) in 1,4-dioxane (3 mL) was added hydrochloric acid (3 mL, 4M: 1,4-dioxane) and the solution was stirred at room temperature for 4 hours. Nitrogen was bubbled through the solution to drive off most of the excess HCl. Concentration under reduced pressure, followed by high vacuum, gave the amine hydrochloride **5** (0.86 g). The excess weight was due to residual 1,4-dioxane.

Step Five: A solution of the amine hydrochloride **5** (0.21 g, 0.8 mmol), and carbonyldiimidazole (0.15 g, 0.9 mmol) in methylene chloride (2 mL) was stirred at room temperature for 30 minutes. A solution of the amine **6** (prepared from Boc-L-Asp(OtBu)-OH following the above reaction sequence) (0.266 g, 0.9 mmol) in methylene chloride (1 mL) was added and the mixture was stirred first at room temperature overnight and then at 40 °C for 1 hour. A standard acid-base work-up, followed by purification by flash chromatography (silica: eluent 3:1 - 2:1 hexanes:ethyl acetate) gave the urea **7** (0.427 g, quant.).

Step Six: To a solution of the urea **7** (0.328 g, 0.6 mmol) in 1,4-dioxane (1 mL) was added hydrochloric acid (1 mL, 4M: 1,4-dioxane) and the solution was stirred at room temperature overnight. A standard aqueous work-up, followed by flash chromatography (silica: chloroform - 9:1 chloroform:methanol) gave the title compound **8** (0.065 g, 37 %). ^{1}H NMR: (400 MHz: DMSO-d_6) δ 1.63 (1H, m), 1.88 (1H, m), 2.01 (3H, s), 2.35-2.60

(4H, m), 2.97 (1H, dd), 3.06 (1H, dd), 3.12 (1H, dd), 3.17 (1H, dd), 3.82 (1H, m), 4.06 (1H, br ddd), 6.01 (1H, d, NH), 6.14 (1H, d, NH), 7.17 (2H, m), 7.30 (4H, m), 7.38 (4H, m).

Example 2

Synthesis of (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[({3-[(2-methylbenzyl)amino]phenyl}thio)methyl]pentyl}oxy)carbonyl]amino} propanoic acid (**15**)

Step One: Copper (I) iodide (0.63 g, 3.3 mmol) was suspended in diethyl ether (100 mL) and chilled to -45 °C under nitrogen. n-Propylmagnesium chloride (16 mL, 1.0 M in diethyl ether, 16.0 mmol) was added slowly to the solution. After 10 minutes, (2S)-(+)-glycidyl tosylate (5.00 g, 21.9 mmol) in diethyl ether (100 mL) was added dropwise *via* cannula over 1 hour. After 5 hours, the mixture was warmed to 0 °C and quenched with saturated, aqueous ammonium chloride (50 mL). The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Compound **9** (5.61 g, 90 %) was recovered as a clear oil and was used without further purification.

Step Two: Compound **9** (1.55 g, 5.7 mmol) was dissolved in DMF (20.5 mL) at room temperature. Potassium carbonate (1.07 g, 7.7 mmol) was added and the suspension was sparged with nitrogen gas for 15 minutes. 3-Aminothiophenol (0.60 mL, 5.7 mmol) was introduced *via* syringe and the solution was stirred overnight. The mixture was diluted with water and ethyl acetate, and the pH of the aqueous layer was adjusted with dilute HCl to pH 5 - 6. The organic layer was washed with water and brine. The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Compound **10** (1.25 g, 98 %) was recovered as a yellow oil and was used

without further purification.

Step Three: Compound **10** (1.25 g, 5.7 mmol) and pyridine (1.3 mL, 15.9 mmol) were dissolved in dichloromethane (23.5 mL) and chilled to 0 °C. The solution was treated with trifluoroacetic anhydride (2.0 mL, 14.1 mmol) and allowed to warm to room temperature overnight. The mixture was washed with 2N HCl, water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Compound **11** (2.05 g, 92 %) was recovered as a yellow oil and was used without further purification.

Step Four: Compound **11** (0.52 g, 1.25 mmol) was dissolved in acetone (5.5 mL). The resulting solution was treated with potassium carbonate and α-bromo-o-xylene (0.40 mL, 3.0 mmol) and refluxed overnight. The mixture was cooled and concentrated under reduced pressure. Purification by chromatography (silica gel, 4:1 hexanes:ethyl acetate) gave **12** (0.36g, 69%).

Step Five: Compound **12** (0.20 g, 0.51 mmol) was dissolved in THF (1.0 mL) and N, N-diisopropylethylamine (0.107 mL, 0.61 mmol) was added. The reaction mixture was chilled to 0 °C under nitrogen, and phosgene (0.32 mL, 20% in toluene) was added *via* syringe. The mixture was stirred 30 minutes at 0 °C, then 2 hours at room temperature and then was recooled to 0 °C. A solution of ethyl 3-amino-3-(3,4-methylenedioxyphenyl)propionate (**13**) (0.13 g, 0.56 mmol) and N, N-diisopropylethylamine (0.107 mL, 0.61 mmol) in THF (1.0 mL) was added by dropwise *via* cannula. The mixture was warmed to room temperature and stirred an additional 1 hour. The mixture was diluted with ethyl acetate and washed with 2N HCl, water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography (silica gel, gradient elution 6:1 to 4:1 hexanes:ethyl acetate) gave **14** (0.19g, 58%).

Step Six: Compound **14** (0.19 g, 0.29 mmol) was dissolved in 3:1 THF/water (1.1 mL) and treated with 2N $NaOH_{(aq)}$ (0.3 mL, 0.6 mmol) and methanol (0.3 mL). After 1 hour at room temperature, the mixture was diluted with water and washed with dichloromethane. The ethyl acetate layer was acidified with excess 2N HCl and washed with ethyl acetate (2x). The organic layers were combined, washed with brine and dried over Na_2SO_4. The organic solution was filtered and concentrated under reduced pressure to give compound **15** (0.15 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (d, J = 7.7 Hz, 1H), 7.26 (dd, 1H), 7.14 (m, 4H), 6.99 (dd, J = 7.9 Hz, 1H), 6.87 (d, J = 1.5 Hz, 1H), 6.79 (d, J = 8.0 Hz 1H), 6.75 (dd, J = 1.5, 8.0 Hz, 1H), 6.58 (br s, 1H), 6.53 (br d, J = 7.3 Hz, 1H), 6.44 (br d, J = 8.0 Hz, 1H), 5.96 (s, 2H), 4.83 (dd, J = 8.0, 15.4 Hz, 1H), 4.67 (m, 1H), 4.21 (s, 2H), 3.0 (m, 2H), 2.63 (dd, J = 8.3, 15.6 Hz, 1H), 2.56 (dd, J = 6.6, 15.4 Hz 1H), 2.32 (s, 3H), 1.61 (m, 1H), 1.49 (m, 1H), 1.18 (m 4H), 0.78 (br, s, 3H).

Example 3

Synthesis of (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(2-thienylmethoxy)methyl]pentyl}amino)carbonyl]amino}propanoic acid (**22**).

Step One: To a solution of (S)-glycidyl tosylate (842 mg, 3.69 mmol) and 2-thiophenemethanol (842 mg, 7.38 mmol) in CH_2Cl_2 (7.4 ml) cooled to 0 °C under a dry nitrogen atmosphere, BF_3●OEt_2 (0.046 ml, 0.37 mmol) was added by syringe. The mixture was warmed to room temperature and stirred 4 days, then concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 3:2 hexanes:ethyl acetate increasing to 1:1 hexanes:ethyl acetate to yield a 2:1 mixture of **16**:(S)-glycidyl tosylate (394 mg) as a light yellow oil.

Step Two: To a solution of a 2:1 mixture of **16**:(S)-glycidyl tosylate (320 mg,

assume 0.73 mmol **16** and 0.37 mmol (S)-glycidyl tosylate) in diethyl ether (22 ml) cooled to -78 °C under a dry nitrogen atmosphere, propylmagnesiumchloride (2.75 ml of a 2.0 M solution in diethyl ether, 5.5 mmol) was added dropwise by syringe. The resulting mixture was stirred at -78 °C for 15 minutes, then was allowed to warm to room temperature, stirred for 1 hour and quenched with saturated NH_4Cl. The mixture was diluted with ethyl acetate and washed with H_2O (2 times), and brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 3:1 hexanes:ethyl acetate to yield **17** (95 mg, 15% for two steps).

Step Three: To a solution of **17** (116 mg, 0.54 mmol) in CH_2Cl_2 (3 ml) at room temperature under a dry nitrogen atmosphere, triethylamine (0.11 ml, 0.81 mmol) and methanesulfonyl chloride (0.053 ml, 0.68 mmol) were added dropwise by syringe. The resulting mixture was stirred for 15 minutes, was diluted with 1:1 hexanes:ethyl acetate and was washed with saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under reduced pressure to give **18** (153 mg) as a light yellow oil. This material was used without purification.

Step Four: To a solution of **18** (150 mg, 0.51 mmol) in DMF (2 ml) cooled to 10 °C under a dry nitrogen atmosphere, sodium azide (66 mg, 1.0 mmol) was added. The resulting mixture was heated to 80 °C stirred for 2 hours, then was cooled to room temperature, diluted with 1:1 hexanes:ethyl acetate and washed with H_2O (3 times) and brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under reduced pressure to give **19** (119 mg, 98 %) as a light yellow oil. This material was used without purification.

Step Five: To a solution of **19** (119 mg, 0.50 mmol) in THF (2 ml) at room temperature under a dry nitrogen atmosphere, H_2O (0.092 ml, 5.1 mmol) and triphenylphosphine (401 mg, 1.53 mmol) were added. The resulting mixture

was stirred for 44 hours at which time TLC indicated only partial conversion. Additional H_2O (0.092 ml, 5.1 mmol) and triphenylphosphine (401 mg, 1.53 mmol) were added and the mixture was stirred for 4 days. The mixture was diluted with CH_2Cl_2 and was washed with approximately a 9:1 mixture of water/saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (2 times) and the combined organic phases were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography, eluting with 19:1 hexanes:ethyl acetate then 19:1 chloroform:methanol to yield **20** (75 mg, 70 %) as a colorless oil.

Step Six: To a solution of **20** (75 mg, 0.35 mmol) in 1,2-dichloroethane (2 ml) at room temperature under a dry nitrogen atmosphere, carbonyldiimidazole (62 mg, 0.38 mmol) was added. The resulting mixture was stirred for 2 hours and N,N-diisopropylethylamine (0.078 ml, 0.45 mmol) and **21** (101 mg, 0.41 mmol) were added. The mixture was heated to reflux for 14 hours, cooled to room temperature, then was diluted with ethyl acetate and was washed with HCl (2N) and brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 9:1 chloroform:methanol then 4:1 chloroform:methanol to yield **22** (70 mg, 45 %) as a pale yellow powder. ^1H NMR (400 MHz, CD_3SOCD_3): δ 0.81 (t, J = 6.6 Hz, 3H), 1.22 (m, 5H), 1.45 (m, 1H), 2.39 (m, 2H), 3.37 (m, overlaps H_2O, 1H), 3.63 (m, 1H), 4.60 (d, J = 12.8 Hz, 1H), 4.64 (d, J = 12.8 Hz, 1H), 4.91 (m, 1H), 5.93 (s overlapping m, 3H), 6.61 (m, 1H), 6.75 (m, 3H), 6.84 (br. s, 1H), 7.02 (m, 2H), 7.49 (d, J = 5.12 Hz, 1H).

Example 4

Synthesis of (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-{[(2-thienylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid (**27**).

Step One: N-α-t-BOC-N-ε-CBZ-L-Lysine (400.0 mg, 1.05 mmol) and thiophene 2-methylamine (0.12 ml, 1.16 mmol) were dissolved in DMF (7 ml). To this was added 1-(3-dimethylaminopropyl)-3 ethylcarbodiimide hydrochloride (222 mg, 1.16 mmol), 1-hydroxybenzotriazole (157.0 mg, 1.16 mmol), and 4-methylmorpholine (0.16 ml, 1.16 mmol). The reaction was then stirred at room temperature for 24 hours. The mixture was taken up in ethyl acetate (200 ml), washed with water (2 x 100 ml), a saturated solution of sodium bicarbonate (100 ml), brine (100 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give compound **23** (451.7 mg, 90%), which was used without further purification.

Step Two: Compound **23** (451 mg, 0.95 mmol) was dissolved in 2 N HCl in dioxane (6 ml) and stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure and the residue was taken up in ethyl acetate (150 ml) and a saturated solution of sodium bicarbonate (150 ml). The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to yield compound **24** (306.9 mg, 94%), which was used without further purification.

Step Three: Compound **24** (128 mg, 0.37 mmol) and compound **25** (150 mg, 0.37 mmol) were dissolved in tetrahydrofuran (3 ml). Triethylamine (0.05 ml, 0.37 mmol) was added and the reaction stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (100 ml) and washed several times with 0.5 N aqueous NaOH (5 x 25 ml), dried over $MgSO_4$, and concentrated under reduced pressure to yield compound **26** (235.3 mg, 99%), which was used without any further purification.

Step Four: Compound **26** (230 mg, 0.36 mmol) was dissolved in methanol (3 ml), water (3 ml), and tetrahydrofuran (3 ml) and to this solution was added lithium hydroxide (45 mg, 1.08 mmol). The reaction was heated to 50 °C and stirred for 24 hours. The mixture was concentrated under reduced pressure and

the residue was taken up in ethyl acetate (100 ml) and 0.5 N aqueous HCl (50 ml). The organic layer was separated, dried over $MgSO_{4,}$, and concentrated under reduced pressure to yield 171.1 mg (78%) of compound **27**. ^1H NMR(400 MHz, DMSO-d_6): δ 8.5-8.6 (m, 1H), 7.3-7.4 (m, 6H), 7.1-7.2 (m, 1H), 6.9-7.0 (m, 2H), 6.85 (s, 1H), 6.7-6.8 (m, 2H), 6.5-6.6 (m, 2H), 5.9 (s, 2H), 5.0 (s, 2H), 4.8-4.9 (m, 1H), 4.3-4.5 (m, 2H), 4.0-4.1 (m, 1H), 2.9-3.0 (m, 2H), 2.4 (m, 2H), 1.5-1.6 (m, 2H), 1.3-1.5 (m, 2H), 1.1-1.3 (m, 2H).

Synthetic procedures similar to those described above may be utilized to obtain the following compounds: 3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-1-[(benzylsulfanyl)methyl]-2-methylpropyl}amino)carbonyl]amino}propanoic acid, 3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(benzylsulfanyl)methyl]-2-methylpropyl}amino)carbonyl]amino}propanoic acid, 3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-methyl-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, 3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(benzylsulfonyl)methyl]-2-methylpropyl}amino)carbonyl]amino}propanoic acid, 3-(1,3-benzodioxol-5-yl)-3-({[((1S)-1-{[(4-methoxybenzyl)amino]carbonyl}-3-methylbutyl)amino]carbonyl}amino)propanoic acid, 3-(1,3-benzodioxol-5-yl)-3-({[((1R)-1-{[(4-methoxybenzyl)amino]carbonyl}-3-methylbutyl)amino]carbonyl}amino)propanoic acid, (3R)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-methyl-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-2-methyl-1-((phenylsulfanyl)methyl)propyl)amino)carbonyl)amino)propanoic acid, (3S)-3-[({[1-{[bis-(phenylsulfanyl)]methyl}-2-methylpropyl]amino}carbonyl)amino]-3-[(3,4-methylenedioxy)phenyl]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-methyl-1-[(phenethylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-({[((1S)-2-methyl-1-{[(3-phenylpropyl)sulfanyl]methyl}propyl)amino]carbonyl}amino)propanoic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-[({4-[(2-toluidinocarbonyl)amino]benzyl}amino)carbonyl]-2-oxa-4,10,12-

triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(4-hydroxyphenethyl)amino]carbonyl}-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-({[2-(2-pyridinyl)ethyl]amino}carbonyl)-2-oxa-4,10,12-triazapentadecan-15-oic acid, 3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-methyl-1-[({4-[(2-toluidinocarbonyl)amino]benzyl}amino)carbonyl]butyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-3-(methylsulfanyl)-1-((phenylsulfanyl)methyl)propyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-methyl-1-[(phenylsulfanyl)methyl]butyl}amino)carbonyl]amino}propanoic acid, (8S,12S)-12-(1,3-benzodioxol-5-yl)-3,10-dioxo-8-((phenylsulfanyl)methyl)-2-oxa-4,9,11-triazatetradecan-14-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-[(phenylsulfanyl)methyl]-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-({[3-(2-oxo-1-pyrrolidinyl)propyl]amino} carbonyl)-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-9-{[(1H-benzimidazol-2-ylmethyl)amino]carbonyl}-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-{[(4-piperidinylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-{[(2-thienylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(3-hydroxy-4-methoxybenzyl)amino]carbonyl}-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(4-hydroxyphenethyl)amino]carbonyl}-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-9-{[(4-aminobenzyl)amino]carbonyl}-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-[(phenylsulfonyl)methyl]-2-oxa-4,10,12-triazapentadecan-15-oic acid,

(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[({4-[bis(2-methylbenzyl)amino]benzyl}amino)carbonyl]-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid, (3S)-3-[({[(1S)-1-({[4-(acetylamino)phenyl]sulfanyl}methyl)-3-(methylsulfanyl)propyl]amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(4-methoxyphenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-[({[(1S)-1-{[(4-aminophenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(4-chlorophenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-[({4-[(benzylsulfonyl)amino]phenyl}sulfanyl)methyl]-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({4-[(methylsulfonyl)amino]phenyl}sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(4-{[(4-methylphenyl)sulfonyl]amino}phenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid, 3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({4-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (2S)-2-({[((1S)-5-{[(benzyloxy)carbonyl]amino}-1-{[(2-thienylmethyl)amino]carbonyl}pentyl)amino]carbonyl}amino)butanedioic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, N,N'-bis[(1S)-1-(1,3-benzodioxol-5-yl)-2-carboxyethyl]urea, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[({4-[(2-methylbenzyl)amino]benzyl}

amino)carbonyl]-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1R)-2-(benzylsulfonyl)-1-((phenylsulfanyl)methyl)ethyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(phenylsulfanyl)methyl]pentyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-(1,3-benzodioxol-5-yl)-3-(tert-butoxy)-3-oxopropyl]amino}carbonyl)amino]propanoic acid, (3S)-3-[({[(1S)-1-{[(2-aminophenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(2-methylphenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(3-methylphenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((2-(phenylsulfanyl)ethylamino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-[(3-phenylpropyl)sulfanyl]-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(phenylsulfanyl)-1-[(propylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino)carbothioyl]amino}propanoic acid, (3S)-4-(methylsulfanyl)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}butanoic acid, (3S)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}-4-(phenylsulfanyl)butanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-methyl-2-(phenylsulfanyl)ethyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(octylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({3-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-3-(methylsulfanyl)-1-(phenoxymethyl)propyl]amino}carbonyl)

amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[(methyl{(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({1-[(phenylsulfanyl)methyl]pentyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({2-(phenylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-[(carboxymethyl)sulfanyl]-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-[({[(1S)-1-{[(3-aminophenyl)thio]methyl}-3-(methylthio)propyl]amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-[({4-[(2-methylbenzyl)amino]phenyl}thio)methyl]-3-(methylthio)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-[({3-[(methylsulfonyl)amino]phenyl}thio)methyl]-3-(methylthio)propyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylthio)-1-[({3-[(propylsulfonyl)amino]phenyl}thio)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-{[({(1S)-2-(allyloxy)-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}-3-(1,3-benzodioxol-5-yl)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzyloxy)-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1R)-1-phenyl-2-(propylthio)ethyl]amino}carbonyl)amino]propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1R)-1-benzyl-2-(propylthio)ethyl)amino)carbonyl)amino)propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(phenylthio)-1-[(phenylthio)methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-4-hydroxy-1-[(phenylthio)methyl]butyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-ethoxy-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(phenethyloxy)-1-

[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-[(cyclopropylmethyl)thio]-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-2-(benzyloxy)-1-[(benzylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-2-(benzyloxy)-1-[(benzylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-2-(benzyloxy)-1-[(ethylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylthio)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzylthio)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[({4-[(2-toluidinocarbonyl)amino]phenyl}thio)methyl]pentyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[({3-[(2-methylbenzyl)amino]phenyl}thio)methyl]pentyl}oxy)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-{[(4-methylphenyl)sulfonyl]amino}-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(2-thienylmethoxy)methyl]pentyl}amino)carbonyl]amino}propanoic acid, and pharmaceutically acceptable salts thereof.

Example 5

A procedure in which a 26-amino acid peptide containing the CS1 sequence of fibronectin with an N-terminal Cys (CDELPQLVTLPHPNLHGPEILDVPST) was coupled to maleimide activated ovalbumin was used to determine the efficacy of the compounds synthesized. Bovine serum albumin (BSA) and CS1 conjugated ovalbumin were coated onto 96-well polystyrene plates at 0.5 μg/ml in TBS (50 mM TRIS, pH 7.5; 150 mM NaCl) at 4°C for 16 hours. The plates were washed three times with TBS and

blocked with TBS containing 3% BSA at room temperature for 4 hours. Blocked plates were washed three times in binding buffer (TBS; 1 mM $MgCl_2$; 1 mM $CaCl_2$; 1 mM $MnCl_2$) prior to assay. Ramos cells fluorescently labeled with calcein AM were resuspended in binding buffer (10^7 cells/ml) and diluted 1:2 with same buffer with or without compound. 100 μM of compound was added. The cells were added immediately to the wells (2.5 x 10^5 cells/well) and incubated for 30 minutes at 37°C. Following three washes with binding buffer, adherent cells were lysed and quantitated using a fluorometer. The results are shown in Table 1. IC_{50} is defined as the dose required to give 50% inhibition. A stands for inhibition in Table 1, and the percent inhibition indicates the inhibition of cell adhesion when compound is included in the assay at a concentration of 100 μm . The lower the IC_{50} value and the greater the percentage of inhibition, the more efficient the compound is at prevention of cell adhesion.

Table 1

Compound	IC_{50}	% A
3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-1-[(benzylsulfanyl)methyl]-2-methylpropyl}amino)carbonyl]amino}propanoic acid	40	83
3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(benzylsulfanyl)methyl]-2-methylpropyl}amino)carbonyl]amino}propanoic acid	10	100
3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-methyl-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	5	99
3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(benzylsulfonyl)methyl]-2-methylpropyl}amino)carbonyl]amino}propanoic acid	35	92
3-(1,3-benzodioxol-5-yl)-3-({[((1S)-1-{[(4-methoxybenzyl)amino]carbonyl}-3-methylbutyl)amino]carbonyl}amino)propanoic acid	0.5	100
3-(1,3-benzodioxol-5-yl)-3-({[((1R)-1-{[(4-methoxybenzyl)amino]carbonyl}-3-methylbutyl)amino]carbonyl}amino)propanoic acid	45	66
(3R)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-methyl-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	35	83
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-2-methyl-1-((phenylsulfanyl)methyl)propyl)amino)carbonyl)amino)propanoic acid	2.5	100
(3S)-3-[({[1-{[bis-(phenylsulfanyl)]methyl}-2-methylpropyl]amino}carbonyl)amino]-3-[(3,4-methylenedioxy)phenyl]propanoic acid	35	95
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-methyl-1-[(phenethylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	20	98
(3S)-3-(1,3-benzodioxol-5-yl)-3-({[((1S)-2-methyl-1-{[(3-phenylpropyl)sulfanyl]methyl}propyl)amino]carbonyl}amino)propanoic acid	20	99
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-[({4-[(2-toluidinocarbonyl)amino]benzyl}amino)carbonyl]-2-oxa-4,10,12-triazapentadecan-15-oic acid	0.0003	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(4-hydroxyphenethyl)amino]carbonyl}-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid	2	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-({[2-(2-pyridinyl)ethyl]amino}carbonyl)-2-oxa-4,10,12-triazapentadecan-15-oic acid	2	100

3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-methyl-1-[({4-[(2-toluidinocarbonyl)amino]benzyl}amino)carbonyl]butyl}amino)carbonyl]amino}propanoic acid	0.02	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	45	78
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-methyl-1-[(phenylsulfanyl)methyl]butyl}amino)carbonyl]amino}propanoic acid	2	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-3-(methylsulfanyl)-1-((phenylsulfanyl)methyl)propyl)amino)carbonyl)amino)propanoic acid	0.3	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-[(phenylsulfanyl)methyl]-2-oxa-4,10,12-triazapentadecan-15-oic acid	0.4	100
(8S, 12S)-12-(1,3-benzodioxol-5-yl)-3,10-dioxo-8-((phenylsulfanyl)methyl)-2-oxa-4,9,11-triazatetradecan-14-oic acid	2	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-({[3-(2-oxo-1-pyrrolidinyl)propyl]amino}carbonyl)-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid	3	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-({[2-(1H-indol-3-yl)ethyl]amino}carbonyl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	3.5	100
(9S,13S)-9-{[(1H-benzimidazol-2-ylmethyl)amino]carbonyl}-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	2	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-{[(4-piperidinylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid	5	97
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-{[(2-thienylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid, **27**	0.2	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(3-hydroxy-4-methoxybenzyl)amino]carbonyl}-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	0.2	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(4-hydroxyphenethyl)amino]carbonyl}-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	6	100
(9S,13S)-9-{[(4-aminobenzyl)amino]carbonyl}-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	0.3	100
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-9-[(phenylsulfonyl)methyl]-2-oxa-4,10,12-triazapentadecan-15-oic acid	>100	20
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[({4-[bis(2-methylbenzyl)amino]benzyl}amino)carbonyl]-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid	1	95
(3S)-3-[({[(1S)-1-({[4-(acetylamino)phenyl]sulfanyl}methyl)-3-(methylsulfanyl)propyl]amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid	3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(4-methoxyphenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid	7	100
(3S)-3-[({[(1S)-1-{[(4-aminophenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid	3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(4-chlorophenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid	3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid	0.02	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-[({4-[(benzylsulfonyl)amino]phenyl}sulfanyl)methyl]-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({4-[(methylsulfonyl)amino]phenyl}sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	0.5	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(4-{[(4-methylphenyl)sulfonyl]amino}phenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid	0.4	100
3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	25	96
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({4-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	0.0009	100
(2S)-2-({[((1S)-5-{[(benzyloxy)carbonyl]amino}-1-{[(2-thienylmethyl)amino]carbonyl}pentyl)amino]carbonyl}amino)butanedioic acid	45	89

(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylsulfanyl)-1-[(phenylsulfanyl)methyl] ethyl}amino)carbonyl]amino}propanoic acid	0.05	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(methylsulfanyl)-1-[(phenylsulfanyl) methyl]ethyl}amino)carbonyl]amino}propanoic acid	0.1	100
N,N'-bis[(1S)-1-(1,3-benzodioxol-5-yl)-2-carboxyethyl]urea	7	99
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[({4-[(2-methylbenzyl)amino]benzyl}amino) carbonyl]-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid	0.0004	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1R)-2-(benzylsulfonyl)-1-((phenylsulfanyl)methyl)ethyl)amino)carbonyl)amino)propanoic acid	1	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(phenylsulfanyl)methyl]pentyl}amino) carbonyl]amino}propanoic acid	0.4	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-(1,3-benzodioxol-5-yl)-3-(tert-butoxy)-3-oxopropyl]amino}carbonyl)amino]propanoic acid	4	100
(3S)-3-[({[(1S)-1-{[(2-aminophenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl] amino}carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(2-methylphenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-{[(3-methylphenyl)sulfanyl]methyl}-3-(methylsulfanyl)propyl]amino}carbonyl)amino]propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[2-(phenylsulfanyl)ethyl]amino}carbonyl)amino] propanoic acid	6	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-[(3-phenylpropyl)sulfanyl]-1-[(phenyl sulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid	2	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(phenylsulfanyl)-1-[(propylsulfanyl) methyl]ethyl}amino)carbonyl]amino}propanoic acid	0.5	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl) methyl]propyl}amino)carbothioyl]amino}propanoic acid	3	100
(3S)-4-(methylsulfanyl)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl] propyl}amino)carbonyl]amino}butanoic acid	8	99
(3S)-3-{[({(1S)-3-(methylsulfanyl)-1-[(phenylsulfanyl)methyl]propyl}amino) carbonyl]amino}-4-(phenylsulfanyl)butanoic acid, **8**	4	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-methyl-2-(phenylsulfanyl)ethyl]amino} carbonyl)amino]propanoic acid	3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(octylsulfanyl)-1-[(phenylsulfanyl)methyl] ethyl}amino)carbonyl]amino}propanoic acid	5	98
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({3-[(2-toluidino carbonyl)amino]phenyl}sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	0.002	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-3-(methylsulfanyl)-1-(phenoxymethyl) propyl]amino}carbonyl)amino]propanoic acid	20	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[(methyl{(1S)-3-(methylsulfanyl)-1-[(phenyl sulfanyl)methyl]propyl}amino)carbonyl]amino}propanoic acid	35	78
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({1-[(phenylsulfanyl)methyl]pentyl}oxy)carbonyl] amino}propanoic acid	6	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({2-(phenylsulfanyl)-1-[(phenylsulfanyl)methyl] ethyl}amino)carbonyl]amino}propanoic acid	1.5	99
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-[(carboxymethyl)sulfanyl]-1-[(phenyl sulfanyl)methyl]ethyl}amino)carbonyl]amino}propanoic acid	2	100
(3S)-3-[({[(1S)-1-{[(3-aminophenyl)thio]methyl}-3-(methylthio)propyl]amino} carbonyl)amino]-3-(1,3-benzodioxol-5-yl)propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-[({4-[(2-methylbenzyl)amino]phenyl}thio) methyl]-3-(methylthio)propyl]amino}carbonyl)amino]propanoic acid	2	93
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1S)-1-[({3-[(methylsulfonyl)amino]phenyl}thio) methyl]-3-(methylthio)propyl]amino}carbonyl)amino]propanoic acid	0.4	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylthio)-1-[({3-[(propyl sulfonyl)amino]phenyl}thio)methyl]propyl}amino)carbonyl]amino}propanoic acid	0.5	100

(3S)-3-{[({(1S)-2-(allyloxy)-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}-3-(1,3-benzodioxol-5-yl)propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzyloxy)-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1R)-1-phenyl-2-(propylthio)ethyl]amino}carbonyl)amino]propanoic acid	25	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-[({[(1R)-1-benzyl-2-(propylthio)ethyl]amino}carbonyl)amino]propanoic acid	2	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(phenylthio)-1-[(phenylthio)methyl]propyl}amino)carbonyl]amino}propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-4-hydroxy-1-[(phenylthio)methyl]butyl}amino)carbonyl]amino}propanoic acid	2	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-ethoxy-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid	5	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(phenethyloxy)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid	4	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-[(cyclopropylmethyl)thio]-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid	0.2	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-2-(benzyloxy)-1-[(benzylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid	1	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-2-(benzyloxy)-1-[(benzylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid	10	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1R)-2-(benzyloxy)-1-[(ethylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid	12	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylthio)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid	1	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzylthio)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino}propanoic acid	3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[({4-[(2-toluidinocarbonyl)amino]phenyl}thio)methyl]pentyl}oxy)carbonyl]amino}propanoic acid	0.3	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[({3-[(2-methylbenzyl)amino]phenyl}thio)methyl]pentyl}oxy)carbonyl]amino}propanoic acid, **15**	25	100
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-{[(4-methylphenyl)sulfonyl]amino}-1-[(phenylthio)methyl]ethyl}amino)carbonyl]amino}propanoic acid	10	98
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-1-[(2-thienylmethoxy)methyl]pentyl}amino)carbonyl]amino}propanoic acid, **22**	1.5	100

All references cited are hereby incorporated by reference.

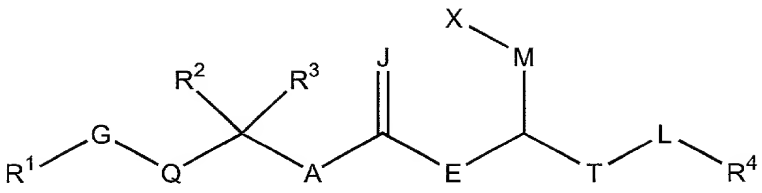
The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:

Claims

We claim:

1. A compound of the structure



wherein A is selected from the group consisting of O, S, and NR^5;

E is selected from the group consisting of CH_2, O, S, and NR^6;

Q is selected from the group consisting of C(O) and $(CH_2)_k$ wherein k is an integer of 0 or 1;

J is selected from the group consisting of O, S and NR^8;

G is selected from the group consisting of O, NH, S, and $(CH_2)_p$ wherein p is an integer of 0 or 1;

T is selected from the group consisting of C(O) and $(CH_2)_b$ wherein b is an integer of from 0 to 3;

L is selected from the group consisting of O, NR^7, S, and $(CH_2)_n$ wherein n is an integer of 0 or 1;

M is selected from the group consisting of $C(R^9)(R^{10})$ and $(CH_2)_u$, wherein u is an integer of from 0 to 3;

X is selected from the group consisting of CO_2B, PO_3H_2, SO_3H, OPO_3H_2, $C(O)NHC(O)R^{11}$, $C(O)NHSO_2R^{12}$, tetrazolyl and hydrogen;

B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl,

aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy, cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl and heterocyclylalkyl groups;

wherein R^2 and R^3 taken together may form a ring;

R^4 and R^7 taken together may form a ring;

R^9 and R^{10} taken together may form a ring;

and salts thereof.

2. A compound of claim 1 wherein

R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, aryl, alkylaryl, arylalkyl, heterocyclyl and alkyl;

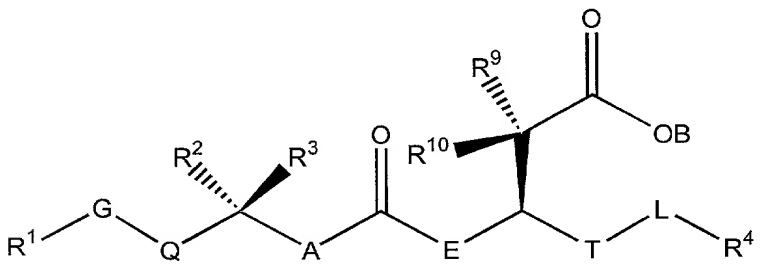
R^4 is selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl and heterocyclylalkyl;

X is CO_2B; and

M is $C(R^9)(R^{10})$ wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen and lower alkyl.

3. A compound of claim 1 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides, and pro-drugs thereof.

4. A compound of claim 1 of the structure



wherein A is selected from the group consisting of O, S, and NR^5;

E is selected from the group consisting of CH_2, O, S, and NR^6;

Q is selected from the group consisting of C(O) and $(CH_2)_k$ wherein k is an integer of 0 or 1;

G is selected from the group consisting of O, NH, S, and $(CH_2)_p$ wherein p is an integer of 0 or 1;

T is selected from the group consisting of C(O) and $(CH_2)_b$ wherein b is an integer of 0 to 3;

L is selected from the group consisting of O, NR^7, S, and $(CH_2)_n$ wherein n is an integer of 0 or 1;

B, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, hydroxyalkyl, alkoxy, alkoxyalkoxy, cycloalkylalkyl, alkylamino, haloalkyl, alkylaryl, arylalkyl, heterocyclyl, alkylheterocyclyl and heterocyclylalkyl groups;

wherein R^2 and R^3 taken together may form a ring;

R^4 and R^7 taken together may form a ring;

R^9 and R^{10} taken together may form a ring;

and salts thereof.

5. A compound of claim 4 wherein R^1, R^2 and R^3 are independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, aryl, alkylaryl, arylalkyl, heterocyclyl and alkyl;

R^4 is selected from the group consisting of aryl, alkylaryl, arylalkyl, heterocyclyl, heterocyclylalkyl and alkyheterocyclyl;

R^5 and R^6 are hydrogen; and

R^9 and R^{10} are independently selected from the group consisting of hydrogen and lower alkyl.

6. A compound of claim 4 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides, and pro-drugs thereof.

7. A compound of claim 1 selected from the group consisting of:
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-3-(methylsulfanyl)-1-((phenylsulfanyl)methyl)propyl)amino) carbonyl)amino)propanoic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-(((((1S)-2-((cyclopropylmethyl)thio)-1-((phenylthio)methyl)ethyl)amino)carbonyl) amino)propanoic acid,
(9S,13S)-13-(1,3-benzodioxol-5-yl)-3,11-dioxo-1-phenyl-9-{[(2-thienylmethyl)amino]carbonyl}-2-oxa-4,10,12-triazapentadecan-15-oic acid, (9S,13S)-13-(1,3-benzodioxol-5-yl)-9-{[(3-hydroxy-4-methoxybenzyl)amino]carbonyl}-3,11-dioxo-2-oxa-4,10,12-triazapentadecan-15-oic acid,
(3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(benzylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino)carbonyl] amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({4-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl) methyl]propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylsulfanyl)-1-[(phenylsulfanyl)methyl]ethyl}amino) carbonyl]amino}propanoic acid,
(9S,13S)-13-(1,3-benzodioxol-5-yl)-9-[({4-[(2-methylbenzyl)amino]benzyl} amino)carbonyl]-3,11-dioxo-1-phenyl-2-oxa-4,10,12-triazapentadecan-15-oic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-3-(methylsulfanyl)-1-[({3-[(2-toluidinocarbonyl)amino]phenyl}sulfanyl)methyl] propyl}amino)carbonyl]amino}propanoic acid, (3S)-3-(1,3-benzodioxol-5-yl)-3-{[({(1S)-2-(ethylthio)-1-[(phenylthio)methyl]ethyl}oxy)carbonyl]amino} propanoic acid, (9S, 13S)-13-(1,3-benxodioxol-5-yl)-3,11-dioxo-1-phenyl-9-(((4-((2-toluidinocarbonyl)amino)benzyl)amino)carbonyl)-2-oxa-4, 10,12-triazapentadecan-15-oic acid,
and pharmaceutically acceptable salts thereof.

8. A compound of claim 7 further comprising derivatives of said compound selected from the group consisting of esters, carbamates, aminals, amides, optical isomers and pro-drugs thereof.

9. A pharmaceutical composition comprising:
a compound of claim 1
and pharmaceutically acceptable salts thereof,
in a pharmaceutically acceptable carrier.

10. A method for selectively inhibiting $\alpha_4\beta_1$ integrin binding in a mammal comprising administering to said mammal a therapeutic amount of a compound of claim 1.

Abstract

A method for the inhibition of the binding of $\alpha_4\beta_1$ integrin to its receptors, for example VCAM-1 (vascular cell adhesion molecule-1) and fibronectin; compounds that inhibit this binding; pharmaceutically active compositions comprising such compounds; and the use of such compounds either as above, or in formulations for the control or prevention of diseases states in which $\alpha_4\beta_1$ is involved.

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

I HEREBY DECLARE THAT:

My residence, post office address, and citizenship are as stated next to my name in PART A on pages 2 and 3 hereof.

I believe I am the original, first, and sole inventor (if only one name is listed) or an original, first, and joint inventor (if plural names are listed) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **Compounds That Inhibit The Binding of Integrins to Their Receptors** the specification of which:

[ ] is attached hereto;

[x] was filed on April 15, 1999 as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to herein.

I acknowledge the duty to disclose all information to the Patent and Trademark Office known to me to be material to patentability of this application, as defined in Title 37, Code of Federal Regulations, Sec. 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate listed in PART B on page 3 hereof and have also identified in PART B on page 3 hereof any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed in PART C on page 3 hereof and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose all information to the Patent and Trademark Office known to me to be material to patentability of this application, as defined in Title 37, Code of Federal Regulations, Sec. 1.56, which became available between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following as my attorneys or agents with full power of substitution to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

Lawrence J. Chapa	Reg. No. 39135	Kathleen A. Lyons	Reg. No. 31,852	Elaine M. Ramesh	Reg. No. 43,032
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See Pages 2 and 3 attached, signed, and made a part hereof.

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

PART A: Inventor Information and Signature

Full name of SOLE or FIRST inventor Ian L. Scott
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First Inventor's signature: _____ Date: _____

Full name of SECOND joint inventor, if any Bore G. Raju
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Second Inventor's signature: _____ Date: _____

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Third Inventor's signature: _____ Date: _____

Full name of FOURTH joint inventor, if any Vanessa O. Grabbe
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Fourth Inventor's signature: _____ Date: _____

Full name of FIFTH joint inventor, if any Jamal Kassir
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Fifth Inventor's signature: _____ Date: _____

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Sixth Inventor's signature: _____ Date: _____

See Pages 1 and 3 attached and made a part hereof.

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

PART A: (Continued)

Full name of SEVENTH joint inventor, if any Timothy P. Kogan (Deceased)
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Eighth Inventor's signature: _____ Date: _____

Full name of NINTH joint inventor, if any Robert V. Market
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Ninth Inventor's signature: _____ Date: _____

Full name of TENTH joint inventor, if any _____
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Post Office Address (If different) _____

Tenth Inventor's signature: _____ Date: _____

PART B: Prior Foreign Application(s)

Serial No.	Country	Day/Month/Year Filed	Priority Claimed
			[ ] Yes [ ] No
			[ ] Yes [ ] No

PART C: Claim for Benefit of Filing Date of Earlier U.S. Application(s)

Serial No.	Filing Date	Status:		
60/082019	April 16, 1998	[ ] Patented	[x] Pending	[ ] Abandoned
		[ ] Patented	[ ] Pending	[ ] Abandoned

See Pages 1 and 2 to which this is attached and from which this Page 3 continues.